PharmaResearch Corporation

Bringing Science to Development

115 N.Third Street, Suite 306 • Wilmington, NC 28401
Tel: (910) 251-9214 • Fax: (910) 251-1545

1989 '99 SEP -1 A9:50

August 3 1, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20857

Re: Draft Guidance for Industry on Establishing Pregnancy Registries Response from Antiretroviral Pregnancy Registry

Docket No. 99D-1541

Dear Sir/Madam:

The Antiretroviral Pregnancy Registry (APR) is a prospective, exposure registration and outcomes registry, which is currently sponsored by seven manufacturers of antiretroviral products with oversight by an Advisory Committee with members from Centers of Disease Control and Prevention (CDC), National Institutes of Health (NIH), as well as specialists in obstetrics and gynecology, teratology, infectious disease, and epidemiology.

The following response to the FDA Draft *Guidance for Industry: Establishing Pregnancy Registries* (Guidelines) is a compilation of comments from the Registry. The comments are grouped by the section indicated in the Draft Guidance document.

Sincerely,

Drew R. Stoudt

Drew R. Stoudt
Senior Director of Regulatory Operations and Compliance

99D-1541

C5

The following sections address responses to individual sections of the *Guidance for Industry: Establishing Pregnancy Registries.*

I. INTRODUCTION

There appears to be an inconsistency in this section. The last sentence states that a registry concept *"is* not appropriate *for known teratogens"*, a concept with which there is agreement. However, in section II. (Background, 3rd paragraph) and section III. (Pregnancy Registries, the last paragraph) seem to recommend the registry concept for such drugs as well.

IV. WHEN IS A PREGNANCY REGISTRY NEEDED?

The Guidelines on page 4 seem to focus on registries for new products *("any product expected to be used common/y by women of reproductive* **potential** *(i.e., especially new molecular entities)'?,* but also maintains a broad-based perspective as suggested on page 5. Here the Guidelines do not *"rule out the potential need for registries of older products or comparative registries of o/d and new products."* Does FDA have definitive thoughts on when a registry is appropriate or does the agency intend for the Guidelines to leave the possibility of registries for both new and old products open?

V. WHEN SHOULD A REGISTRY BE ESTABLISHED?

This section includes more than the title would indicate, perhaps a more descriptive title for the section might be **"V. TIMING, RATIONALE, AND SCOPE OF ESTABLISHING A REGISTRY".**

International Scope

We agree that expanding recruitment internationally would add to the strength of the Registry. However, legislation related to data privacy may disallow transfer of medical records outside the country to a pregnancy registry. In addition, voluntary reporting and follow-up may be problematic in some instances.

VI. WHAT DOES A WELL-DESIGNED REGISTRY LOOK LIKE?

A. Background Information

Background information to be included in this section, especially for products such as antiretrovirals, is constantly changing and would require frequent update. Inclusion of information and projections concerning use and other information requested in the last 3 paragraphs of this section is generally not available and not reliable. Furthermore, estimates of potential off-label use would be inappropriate. Our concerns about these requests are compounded for combination therapy.

B. Description of research methods

1. Patient Recruitment

Distribution of information

The Guidelines calls for wide dissemination of materials to recruit potential registry patients. Suggestions include websites, professional journals, consumer magazines, booths at conference exhibits, and direct mailings to physicians and possibly patients. In accordance with the Guidelines, all materials must be reviewed and cleared by the FDA reviewing division and DDMAC (Division of Drug Marketing and Communication).

- DDMAC review of materials for products where the indication for use is not approved may be required. However, approval for production and broad distribution of informational materials to providers and organizations, who can contribute and assist in recruitment process, will be necessary.

- If the agency is advancing the cause of registries in general, perhaps DDMAC restrictions could be relaxed, for example, allowing distribution of some materials without full prescribing information. APR includes sponsors representing 14 products, some with multiple formulations. Distribution of a one page flyer or brochure with package inserts for all of these products is not helpful to clinicians and increases the production and broad distribution costs.
- Since this review process has the potential to be lengthy, we request that the Guidelines specify a review period for these materials and clarify whether final comment and approval will ultimately come from the reviewing division or DDMAC. Since recruitment materials may not be considered as promotional, the reviewing division may 'be the appropriate authority to provide comment.

In summary, guidelines including very specific details on what types of "promotion" are allowed and how they should be carried out and by whom is needed, as well as definition of the timing for the review and approval process.

Enrollment through clinicians vs. patients

Enrollment directly through the pregnant woman may be appropriate for some registries, as the lost to follow-up rate may be lower. However, there are women who choose not to enroll themselves or for whom there are barriers to self-enrollment, but who would be willing for others to participate for them. Therefore collecting information through the providers should not be discounted. In addition, diagnoses and attribution would require medical verification.

2. Eligibility Requirements

Timing of enrollment:

The Guidelines states that *"women should be enrolled in a registry after exposure to a product prior to and/or during pregnancy".* This would require enrolling all women of childbearing potential at the start of any therapy, which is not feasible. It is also reported in the Guidelines that 60% of pregnancies are unplanned which means that a considerable amount of unused data and failure in agreement on interpretation of results would likely be forthcoming. A study of this magnitude and duration would be cost prohibitive.

Regulatory Reporting:

Reporting requirements for pregnancy registries are extremely important and complex, and therefore should be specifically defined in a separate section. The Guidelines should include reporting requirements for single cases as well as for periodic reports.

The last paragraph in this section on page 9 states: *'Sponsors are required to report spontaneous reports of serious adverse outcomes, such* as *birth defects, to the FDA when identified during the recruitment process even if such reports* are *not included in the pregnancy registry analysis (21CFR 314.80). However, these reports should be identified as having been reported to the registry. Waivers of the specific* time *frames and methods for fhis requirement with proposed* alternative *reporting plans may be requested for individual registries. "*

Reports to the Registry

- Event reports, reported to the registry are collected during active recruitment of the patient into the registry. Such reports should be considered solicited as the information is obtained "during planned contacts and active solicitation of information from patients." (See *Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drug and Licensed* Biological *Products: Clarification* of *What to Report, August* 1997, *pp.* 3-4.) Under solicited report guidance, the events would be then reported as information obtained from a postmarketing study and only submitted to the FDA if serious, unexpected, and related to the drug. The attribution of the event would be difficult to obtain from the patient alone, in the absence of confirmation from the health care provider.

Subgroup Analysis

The Guidelines stipulates in Section V. that recruitment efforts should be made to ensure that a *"heterogeneous"* group of patients is studied, allowing analysis of various demographic subgroups, severity of disease, and length of treatment. A considerably large group of patients would have to be recruited and followed just to allow for detection of increased risk potential for various outcomes (spontaneous abortion, major birth defects, specific abnormalities or syndromes). It is highly unlikely that sufficient numbers of pregnant patients could be recruited to detect statistically significant differences among subgroups.

Time **To** Complete

It is very difficult to predict a time frame for completion. A sample size sufficient to detect an increase in the outcome of interest is more appropriate than a time frame for completion, which is difficult to predict.

Paternal Exposures

The Guidelines do not address a registry for men in situations where only the father is receiving medication. Baseline information and follow-up on the outcome of the pregnancy would be difficult to obtain.

VII. REPORTING RESULTS

Page 14. Capturing of maternal adverse events is beyond the scope of most registries. Systematic collection of both the maternal and fetal outcomes makes data collection and powering of the study problematic.

As stated above in Section VI.B.l. Patient Recruitment, there is concern with the suggested regulatory reporting procedure of submitting reports made to the registry as spontaneous reports. This procedure contradicts the guidelines for AE reporting updated in August, 1997, which indicate that *"for the purposes of postmarketing* safety *reporting under 21 CFR 310.305, 314.80, 314.98 and 600.80, that information concerning potential adverse experiences derived during planned contacts and* active *solicitation of information from patients (e.g., company-sponsored patient support programs, disease management programs) should be handled as safety information obtained from a postmarketing study. Applicants, manufacturers, and licensed manufacturers should not report safefy information obtained through these types of patient contacts unless the adverse event meets regulatory definitions of serious and unexpected and there is a reasonable possibility that the drug or biological product caused the adverse experience".* In addition, this reporting procedure is inconsistent with ICH guidelines, which clearly defines spontaneous reports as unsolicited reports.

- Reporting of adverse events from pregnancy registries has not been addressed at all by the regulations. Guidance from FDA personnel via personal communication has been inconsistent. Not all sponsors handle registry reports as coming from "postmarketing surveillance studies." If they are to be considered by all as postmarketing surveillance studies, it is not appropriate that the reporting requirements be subject to 15-Day alert reporting. Instead, those reports would be included in the current regulations for postmarketing studies (21 CFR § 314.80 (2) (e) requiring a serious, unexpected event that the applicant *"concludes that there is* a *reasonable possibility that the drug* caused *the adverse experience."* Postmarketing studies are not subject to periodic reporting, except for 15-day alerts, and this should not be different for registry reports. If registries were required to submit interim and annual reports, sponsor periodic reporting of these adverse experience reports would be redundant and potentially evaluated out of the context of the registry.
- Again, waivers should be discouraged. The included reference, 21CFR 314.90, gives information on waivers, for well-controlled studies, that are submitted as part of a drug application.
- Pregnancy registries are not intended to enhance postmarketing surveillance. Registries should be considered an unbiased, separate entity with entirely different safety purposes. The Agency should consider establishing entirely new reporting requirement for registries, rather than to apply confusing,

modified, combination (spontaneous and postmarketing studies) regulations to existing or newly-established pregnancy registries.

Interim Reporting

- The Guidelines for the minimal information that should be reported in interim reports is too extensive and not relevant.
- The percent of abortions should be stratified by when reported (week reported) not when occurred.

VIII. **OTHER CONSIDERATIONS AND ADDITIONAL STUDIES**

The Guidelines should elaborate on what is meant by *"referral bias"* and what impact that bias might have on the results. Regarding automated databases, it is almost impossible to find enough pregnancy exposure data in any automated database unless the drug is used extremely widely, especially early in the market.

ATTACHMENT 1: SUGGESTED DATA ELEMENTS FOR PREGNANCY REGISTRIES

The number of *"minima/"* data elements proposed for collection is extensive (see comments on page 4 discussion of Minimum Criteria). The expectation that a patient (as well as any control group) will routinely provide complete and detailed information on medical and ob/gyn history, and personal information, such as the occupation of family members *seems* excessive and may actually be a deterrent to voluntary enrollment. These data would not be of value in any comparative study or subgroup analyses if it is not possible to routinely fill all data fields.

If the primary contact for registries is the enrolled patient, it is doubtful that this level of information could be collected. Even if the contact were a health care professional, this amount of data would be prohibitive to encouraging enrollment and data collection.

OTHER ITEMS NOT ADDRESSED IN THE GUIDANCE DOCUMENT

Multiple Sponsors

The Guidelines do not address the situation where a pregnancy registry for a given disease or condition is supported by multiple sponsors. The Guidelines do not stipulate how sponsors should apply for waivers. For example, for a multi-sponsor registry would each sponsor be required to request a waiver? Would there be possibility that one sponsor would receive a waiver from a particular item and another one not? Meeting the different requirements for a number of sponsors can be complex and costly. What happens in the case of a sponsor joining an existing registry as a new member?

In addition, since the Guidelines suggest that new products are more likely to be targeted for establishment of a registry than already marketed products, the new product may be placed at a competitive disadvantage if broad recruitment efforts for the newly approved product elicit undue alarm in patients about the potential for negative pregnancy outcomes.

Combination Therapy

Monotherapy is not used to treat HIV. The effects of many approved antiretroviral medications in early pregnancy are unknown. It would be difficult to discern what individual component of a regimen contributed to the outcome, or whether the outcome was the result of a particular combination.

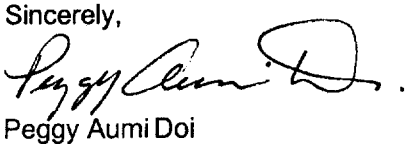
Physical Liability

Physicians may be reluctant to participate in a pregnancy registry because it could represent a liability for them as prescribers of the medication, in the event of a poor pregnancy outcome.

IN SUMMARY

The APR Sponsors and Advisory Committee appreciate the opportunity to comment on these draft Guidelines. We recognize the difficulty of developing guidelines that are specific enough to be useful, but general enough to cover all diseases for all registries. The Sponsors and Advisory Committee participants strongly suggest that FDA seek further input, perhaps in a public forum, of those with experience with pregnancy registries of various designs, prior to issuing the final set of Guidelines.

Sincerely,



Peggy Aumi Doi
Director, Expanded Access Programs
PharmaResearch Corporation
phone: 910-254-4915, email: doip@pharmaresearch.com

LETTER

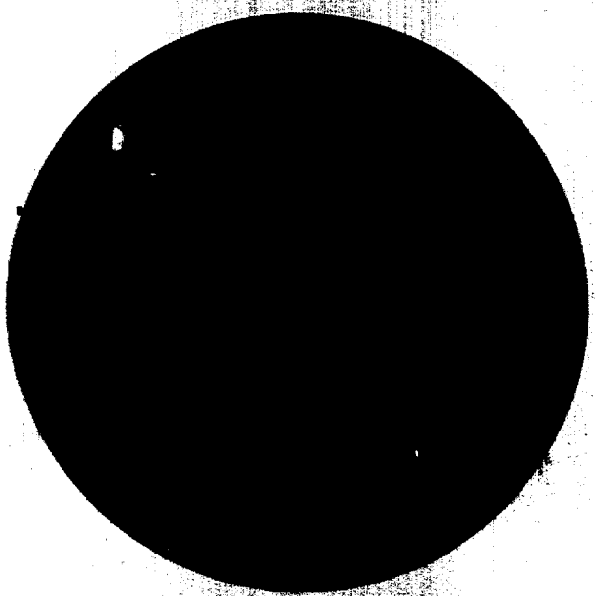
Call 1-800-PICK-UPS (1-800-742-5877) or visit our Web site at www.ups.com

ace Labels in This Space

otions: 1 UPS Tracking Label and your address label
Place the Tracking Label to the left of the address label.
Stamp your UPS Shipper Number or place parcel register tape above the address label.

2 UPS Air Shipping Document

3 UPS Waybill



PHARMA RESEARCH
(910)251-9214
115 N. 3RD ST
WILMINGTON NC 28401-1341

SHIP TO: DOCKETS MANAGEMENT BRANCH (HFA-305)
FOOD AND DRUG ADMINISTRATION
DOCKET NUMBER 99D-154 (301)594-5468
ROOM 1061
5630 FISHERS LA.
ROCKVILLE MD 20857

MD 2070-10

UPS NEXT DAY AI 1

TRACKING #: 1Z A0R 974 01 4399 06

PROJ/DEPT:GLAX004/PATREG24/
SENDER:PEGGY DOI

International Shipping Notice - Carriage hereunder may be subject to the rules relating to liability and other terms and/or conditions established by the Convention for the Unification of Certain Rules Relating to International Carriage by Air (the "Warsaw Convention") and/or the Convention on the Contract for the International Carriage of Goods by Road (the "CMR Convention"). These commodities, technology or software were exported from the U.S. in accordance with the Export Administration Regulations. Diversion contrary to U.S. law prohibited. For stopping places, call 1-800-782-7892.

ternational Shipping Notice – Carriage hereunder may be subject to the rules relating to liability and other terms and/or conditions established by the Convention for the Unification of Certain Rules Relating to International Carriage by Air (the "Warsaw Convention") and/or the Convention on the Contract for the International arriage of Goods by Road (the "CMR Convention"). These commodities, technology or software were exported from the U.S. in accordance with the Export Administration Regulations. Diversion contrary to U.S. law prohibited. For stopping places, call 1-800-782-7892.